IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Alan BERRY et al.	Group Art Unit: 1652
Application No.: 09/341,600	Examiner: Christian L. Fronda
Filed: September 15, 1999	Confirmation No.: 5327
Attorney Docket No.: 3161-18-PUS	PRE-APPEAL BRIEF REQUEST FOR REVIEW
For: PROCESS FOR PRODUCTION OF N-GLUCOSAMINE	***Submitted Via Electronic Filing***

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Status of the Claims

Applicants respectfully request a pre-appeal brief review of the claim rejections in the final Office Action mailed May 2, 2007. This request is being filed with a Notice of Appeal. Claims 40-72 and 74-91 are currently pending in this application, while claims 1-39 and 73 were previously canceled. No claim amendments are presented with this filing. This request for review focuses on the rejection of claims 40-70, 72, 74-77 and 80-91 under 35 U.S.C. § 112, First Paragraph, and claims 40, 53, 55, 62-64, 71, 75, 76-79 and 87-89 under 35 U.S.C. § 102(b).

Grounds for Traversing Final Rejection

The Examiner rejected claims 40-70, 72, 74-77 and 80-91 under 35 U.S.C. § 112, First Paragraph, as failing to comply with the enablement requirement. In addition, the Examiner rejected claims 40, 53, 55, 62-64, 71, 75, 76-79 and 87-89 under 35 U.S.C. § 102(b) as being anticipated by Dutka-Malen et al. Applicants respectfully submit that these rejections constitute clear errors for the reasons set forth below.

A. The Specification Provides Enabling Support for the Full Scope of Claims 40-70, 72, 74-77 and 80-91

Claims 40-70, 72, 74-77 and 80-91 were rejected under 35 U.S.C. § 112, First Paragraph, as failing to comply with the enablement requirement. According to the Office, the specification does not provide guidance regarding the specific type of genetic modification to perform on the specific codons within the coding region of a polynucleotide encoding glucosamine-6-phosphate synthase. Office Action dated May 2, 2007, at 3-4. Applicants traverse this rejection.

To satisfy the enablement requirement, the specification must contain sufficient disclosure to enable one skilled in the art to make and use the claimed invention without undue experimentation. M.P.E.P. § 2164. A determination of whether the claims are enabled thus involves, *inter alia*, the level of skill in the art and the amount of direction provided by the inventor. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Applicants submit that the specification provides sufficient disclosure to allow one of skill in the art to practice the full scope of the claims.

The present claims do not recite specific sequences of glucosamine-6-phosphate synthases, i.e., sequences with specific amino acid mutations. Rather, the claims recite a bacterium or yeast that comprises at least one genetic modification that increases the activity of glucosamine-6-phosphate synthase compared to the unmodified glucosamine-6-phosphate synthase.

The specification specifically exemplifies the making of bacteria that express a recombinant nucleic acid molecule encoding a bacterial or yeast glucosamine-6-phosphate synthase. The inventors also disclose the production of at least three bacterial strains that express a recombinant nucleic acid molecule encoding a bacterial or yeast glucosamine-6-phosphate synthase, wherein said synthase comprises a genetic modification that reduces the glucosamine-6-phosphate product inhibition of said glucosamine-6-phosphate synthase compared to the unmodified enzyme.

The specification further discloses that the invention, while exemplified in bacteria, can be applied to other microorganisms. The amino sugar metabolic pathways and genes and proteins involved therein are known in the art for many bacteria and yeast. Indeed, the Examiner has recognized that bacterial or yeast glucosamine-6-phosphate synthases can be used in the claimed methods. E.g., Office

Action dated April 21, 2005, at 3-5. Thus, Applicants submit that the specification provides enabling support for the claims.

Applicants reiterate the previous arguments concerning the amount of experimentation involved to make and use the bacterial or yeast glucosamine-6-phosphate synthases with the recited genetic modifications. The present inventors have exemplified the production of bacteria expressing these glucosamine-6-phosphate synthases. The Examiner refers to Guo et al. to support his assertion that only a small percentage of possible modifications would increase synthase activity, and the claimed invention thus requires "finding a few mutants within several billion or more." Office Action dated May 2, 2007, at 3.

However, Applicants submit that this argument is completely contrary to what has been clearly exemplified and described in the present specification and in subsequent declarations and arguments, and further, goes beyond what is actually required by the present claims. In fact, the inventors have demonstrated that in one routine experiment using the methods of the instant claims, not one, not ten, but **96** microorganisms out of 4368 microorganisms were identified as producers of excess glucosamine compared to the parent strain (see, e.g., Example 5). This is hardly equivalent to needing to find "a few mutants within several billion or more". Thus, Applicants have clearly demonstrated the production and routine selection of the microorganisms recited in the claims.

The Examiner asserts that finding a synthase with 25 or 50 mutations would not be possible. *Id.* The instant claims, however, do not recite a mutated synthase having 25 or 50 mutations. Rather, the claims only require that the synthase contain a modification sufficient to increase the synthase activity as compared to the unmodified synthase. Applicants have demonstrated that using current techniques in the art (i.e., high throughput mutagenesis and screening techniques), this result is readily achievable, *requires only routine experimentation, and does not take a long time to accomplish*. Applicants submit that these teachings provide sufficient guidance to carry out the methods recited in the instant claims without undue experimentation.

The Examiner continues to argue that it is necessary to know what domains and motifs within the amino acid sequence of the *E. coli* glucosamine-6-phosphate synthase can be modified to make a synthase with increased activity. However, the specification, the Declaration of Dr. Deng, and the Declaration of Dr. Demain have provided

substantial evidence that this is simply not an accurate statement. The Examiner has not provided a specific rebuttal of these arguments or of the evidence provided by Applicants, particularly with respect to the Declaration of Dr. Demain, which included significant evidence that knowledge of the specific domains and motifs within a sequence are not necessary to routinely make and use genetically modified microorganisms as claimed. The Examiner has not provided clear and convincing proof that undue experimentation would be required to make and use the invention in view of the substantial evidence presented to the contrary.

Combining the teachings of the specification with the knowledge in the art at the priority date of the application, one of skill in the art could readily make and use the full scope of the claimed invention without undue experimentation. Therefore, the enablement requirement of 35 U.S.C. § 112, First Paragraph, has been satisfied. Applicants thus respectfully request that these rejections by withdrawn.

B. Dutka-Malen et al. Does Not Teach or Suggest Each Element of Claims 40, 53, 55, 62-64, 71, 75, 76-79 and 87-89

The Examiner rejected claims 40, 53, 55, 62-64, 71, 75, 76-79 and 87-89 under 35 U.S.C. § 102(b) as being anticipated by Dutka-Malen et al. ("Dutka"). The Examiner specifically asserts that:

> Since the process steps taught by Dutka-Malen et al. are the same as the recited process steps, then the process would produce glucosamine and the harvesting of the cells by centrifugation would result in the recovery of the produced glucosamine in the remaining culture media.

Office Action dated May 2, 2007, at 4.

To anticipate a claim, a reference must disclose each and every element set forth in the claim. M.P.E.P. § 2131. For the reasons set forth below, Dutka fails to teach or suggest each element of the claims, and thus cannot possibly anticipate the claims.

Applicants submit that Dutka does not teach that a step of culturing produces and accumulates a product selected from the group consisting of glucosamine-6-phosphate and glucosamine, as recited in the instant claims. At best, Dutka only teaches a molecule encoding the wild-type glucosamine-6-phosphate synthase. Dutka <u>does not measure</u> any glucosamine produced by the microorganism, and does not provide any evidence that the expression of their recombinant nucleic acid molecule increases

production of glucosamine by the microorganism. Dutka does not teach or suggest even attempting to *detect* whether the *E. coli* actually produce glucosamine-6-phosphate or glucosamine, let alone the *recovery* of either product.

Moreover, Dutka does not teach a method for producing glucosamine-6-phosphate or glucosamine, let alone the methods recited in the instant claims. The Examiner has repeatedly admitted this fact during the prosecution of the application. Office Action dated May 26, 2000, at 2, 4, and 5. Indeed, Dutka is directed to the cloning of the *glmS* gene and the investigation of the catalytic properties of the enzyme through *in vitro* methodology (See page 288, col. 1, second full paragraph). In short, Dutka is devoid of any suggestion of a method to produce glucosamine-6-phosphate or glucosamine by fermentation and/or to recover such products from a fermentation medium. Each of these elements is recited in the instant claims.

Thus, at least because Dutka does not teach or suggest a method to produce glucosamine by fermentation according to the steps recited in the instant claims, nor the recovery of either glucosamine-6-phosphate or glucosamine from the culture, Dutka does not teach each and every element set forth in the claims. Accordingly, Dutka does not anticipate claims 40, 53, 55, 62-64, 71, 75, 76-79 and 87-89. Applicants thus respectfully request that these rejections by withdrawn.

For at least the reasons discussed above, there are clear errors in the Examiner's rejections and Applicants respectfully request that they be withdrawn.

The required one-month extension of time fee of $120.00 is submitted herewith via EFS-Web. The one-month extension of time extends the time for reply to September 3, 2007 (September 2, 2007, being a Sunday). In the event that additional fees are due, please debit Deposit Account No. 19-1970.

Respectfully submitted,

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Dated: August 29, 2007

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